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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,698	02/13/2002	Maria Alexandra Glucksmann	MNI-204CP2DV1	4059

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INTELLECTUAL PROPERTY GROUP
MILLENNIUM PHARMACEUTICALS, INC.
75 SIDNEY STREET
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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 02/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,698	GLUCKSMANN ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *n/a*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *24-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *070902*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Claims 24-50 are pending and under examination.

Information Disclosure Statement

The information disclosure statement filed July 9, 2002 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because citations A9 and A12 lack sufficient description so as to lead the reader to the cited documents. The documents provided have been considered, however the citation will not be printed. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Drawings

The drawings filed July 5, 2002 are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: e.g. Fig 1A, 1B, 1C, for example. The specification should refer to each part of the figure. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate

prior version of the sheet, even if only one figure is being amended. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Sequence Disclosures

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons: the specification makes reference to specific polynucleotide and polypeptide sequences, see Fig 1A, for example; these references must contain a sequence identifier of the form: SEQ ID NO: X. A sequence identifier corresponding to a sequence disclosed in a Figure may be located in either the figure itself or in the Brief Description of the Drawings section of the specification. Appropriate correction is required.

Objections:

The disclosure is objected to because of the following informalities:

The specification is missing ATCC deposit numbers, e.g. page 4.

The disclosure is objected to because it contains an embedded hyper-link and/or other form of browser-executable code; see page 20 for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP 608.01(p).

The attempt to incorporate subject matter into this application by reference to active Internet sites (i.e., hyperlinks) is improper because such web sites are constantly being changed and updated. A change or update of the web site would automatically raise the issue of new matter, because the updated information was not known to the inventors at the time of the filing of the instant specification. Also, the organization, views and accuracy of the information contained on commercial web sites is not under the control of the PTO. These references must be removed before the application is allowed, because the printer will not permit the application to go to issue with active web Internet sites listed in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-33 and 37-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims require "a complement thereof". The term "a complement of" is used ambiguously in the art and it may or may not denote a polynucleotide that is perfectly

complementary to a reference polynucleotide as it may also refer broadly to any polynucleotide that may form complementary binding to the reference polynucleotide under an unspecified set of conditions. Thus, without any specific definition provided by the specification, the artisan could not reasonably know whether or not a given polynucleotide would be encompassed by the claims. Additionally, it is noted that the phrase "a complement thereof" places no size limitations on the claimed nucleic acid molecule.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling polynucleotides encoding a polypeptide of SEQ ID NO: 1 and 4 and for naturally occurring polynucleotides that hybridize under the conditions recited at page 44 lines 19 and 20 to the polynucleotides of SEQ ID NO: 2 and 5 wherein elevated levels of said naturally occurring polynucleotides are indicative of cardiac myocyte hypertrophy, does not reasonably provide enablement for polynucleotides comprising complements of said polynucleotides, that do not hybridize as described above.

Claims 24-33 and 37-50 require complements of a polynucleotide of SEQ ID NO: 2 or 5 or that deposited as Acc. No. PTA-1143. As set forth above a complement need not be a full length complement nor a perfectly matched complement. Claims 34-36 require that the polynucleotides be 95% identical to SEQ ID NO: 2 or 5. Thus the claims encompass an

astronomically large genus of polynucleotide variants of SEQ ID NO: 2 and 5, yet the specification has not taught which of these would be useful in the manners described in the specification. The specification indicates that the expression of the polynucleotides of the instant invention (presumably SEQ ID NO: 2 and 5) correlate with hypertrophic cardiac myocytes, page 47, thus the polynucleotides could be useful as hybridization probes to monitor receptor nucleic acid expression, e.g. page 49. The specification provides general guidelines as to how to obtain polynucleotides that specifically bind to SEQ ID NOs: 2 and 5, but does not provide any specific guidelines, nor examples, to enable the skilled artisan to determine which polynucleotides, of the practically limitless number encompassed by the claims, could be used to specifically detect the presence of SEQ ID NO: 2 of 5, and nor has the specification provided guidance as to how to use the claimed polynucleotides that would be expected to specifically bind to polynucleotides other than SEQ ID NOs: 2 and 5.

The state of the prior art as exemplified by Wallace et al., In Abelson and Simon eds., Methods Enzymol. 152(432-443)1987 and Sambrook et al. eds. Molecular Cloning, 1989, Cold Spring Harbor, NY, p.1147 is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Furthermore, a database search was done for oligomers of SEQ ID NO: 2 and 5, and the results suggest that some of the probes encompassed by the claims would not preferentially hybridize to RNA or DNA of SEQ ID NO: 2 or 5, see U.S. Patent No: 5789223 SEQ ID NO: 7 discussed below, for example. Since the claims merely require that the nucleic acid sequence *comprise* a complement of the disclosed polynucleotides, the claims encompass any random sequence of any length as long as it has a portion that is complementary to SEQ ID

NO: 2 or 5. In view of this, the empirical and unpredictable nature of the art, the lack of guidance with respect to appropriate modifications and the lack of guidance as to how to use methods employing other probes that fall within the scope of the claims, the specification does not teach one skilled in the art how to successfully use probes of the claimed scope without undue experimentation.

Further, claims 38-50 require polynucleotides encoding polypeptides comprising only portions of SEQ ID NO: 1 or 4 or only portions of the polynucleotide of 2 or 5. Also claims 34-36 require polynucleotides that need only have 95% identity with the disclosed polynucleotides. Thus, the vast majority of encoded polypeptides are amino acid sequence variants of SEQ ID NO: 1 and 4, i.e. amino acid substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 1 and 4, yet the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, the Applicant has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 1 and 4 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 1 and 4 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 1 and 4 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 1 and 4, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 1 and 4. Conversely, if a protein variant of SEQ ID

NO: 1 and 4 need not have a disclosed property, the specification has failed to teach how to use such a variant.

The specification has not provided a working example of the use of a variant of the polypeptide of SEQ ID NO: 1 and 4nor sufficient guidance so as to enable one of skill in the art to make such a variant. The specification has failed to teach which amino acids of SEQ ID NO: 1 and 4 could be modified so as to produce a polypeptide that is not identical to SEQ ID NO: 1 and 4 and still retain the activity of the polypeptide of SEQ ID NO: 1 and 4- which is to apparently not known.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical

determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 1 and 4 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

Although the specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the infinite number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on

protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 32-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The invention appears to employ novel nucleic acid molecules (i.e. deposited as Acc. No. PTA-1143). Since the nucleic acid molecules are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the nucleic acid molecules are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the nucleic acid molecules. There is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific nucleic acid molecules have been deposited under the Budapest Treaty and that the nucleic acid molecules will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;
(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and
(e) the deposit will be replaced if it should ever become inviable. Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination."

Applicant is advised that the address for the ATCC has recently changed, and that the new address should appear in the specification. The new address is:

American Type Culture Collection

10801 University Boulevard

Manassas, VA 20110-2209

Claims 24-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a human and murine polynucleotide of SEQ ID NO: 2 and 5, respectively, yet the claims encompass polynucleotides not described in the specification, i.e. polynucleotides sequences from other species, mutated sequences, allelic variants, or sequences need that need only be 95% identical to SEQ ID NO: 2 or 5. The specification contemplates

these variants, see page 47-53; none of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. The skilled artisan would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide from a human and a single polynucleotide from a mouse, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, only two naturally occurring polynucleotide sequences, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

With the exception of the human and murine polynucleotides referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed variants, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only human and murine polynucleotides and polynucleotides consisting of fragments thereof, but not the full breadth of the claim meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 24, 26, 28, 30, 32, 33, 38, and 50 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No: 5789223.

U.S. Patent No: 5789223 discloses a polynucleotide that is 100% identical to the instant SEQ ID NO: 2 over a region of 45 base pairs. Positions 1527-1571 of the instant SEQ ID NO: 2 are identical to positions 4083-4039 of 5789223-7, and would thus be considered an isolated

polynucleotide comprising a complement of SEQ ID NO: 2, and presumably the polynucleotide deposited as PTA-1143 as well. Further, given the broadest reasonable interpretation of the word "kit" the U.S. Patent No: 5789223 provides the polynucleotides of claim 50 and instructions for use.

Claims 25, 27, 29, 31, 39-41 are rejected under 35 U.S.C. 102(e) as being anticipated by GenBank Accession number AA030752, published August 21, 1996.

GenBank Accession number AA030752 discloses an isolated polynucleotide that is 100% identical to the instant SEQ ID NO: 5 form position 904-1075, and would thus be considered a complement of SEQ ID NO: 5.

Conclusion

Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached at (571) 272-0829. Official papers filed by fax should be directed to 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

MB

January 29, 2005